Short Communication

The Effect of β-Carotene Supplementation on Serum Vitamin D Metabolite Concentrations[1]

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Abstract

In the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) study, a large randomized placebo-controlled trial designed to test the cancer prevention effects of α-tocopherol (50 mg/day) and β-carotene (20 mg/day), participants receiving supplemental β-carotene had significantly higher rates of lung cancer than those not receiving β-carotene. It has been hypothesized that the supplemental β-carotene may have interfered with the synthesis of vitamin D and that the resulting lower concentrations of vitamin D contributed to the elevated cancer incidence. We evaluated whether supplementation with β-carotene altered the serum concentrations of either 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D in the ATBC Study, by comparing on-study changes between baseline and follow-up serum samples among 20 randomly selected matched pairs of subjects from the β-carotene and placebo groups. In a matched-pair analysis, the difference between the changes in both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in the β-carotene supplement and placebo groups were small and statistically nonsignificant. These results provide no evidence that β-carotene supplementation interferes with the endogenous production of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D and suggest that it is unlikely that an interaction between supplemental β-carotene and vitamin D metabolites contributed to the modest increase in lung cancer incidence observed in the ATBC Study.

Introduction

The ATBC study[3] was a large randomized placebo-controlled trial of male Finnish smokers designed to test the preventive effects of daily supplementation with α-tocopherol (50 mg/day) and β-carotene (20 mg/day) for 5–8 years on the incidence of lung and other cancers (1). At the end of the trial, those who received supplemental β-carotene had significantly higher rates of lung cancer compared with those who did not (change in incidence, 16%; 95% confidence intervals, 2–33%; Refs. 1, 2). Another randomized, double-blinded, placebo-controlled chemoprevention trial, the β-Carotene and Retinol Efficacy Trial (CARET; Ref. 3), which tested β-carotene in combination with retinyl palmitate in smokers and subjects exposed to asbestos, also found elevated lung cancer incidence among those receiving β-carotene and retinol. The biological explanation for these unexpected adverse findings remains unclear.

Kritchevsky *et al.* (4) hypothesize that the observed increase in lung cancer incidence may have reflected an unanticipated interference by β-carotene with the synthesis of vitamin D, the latter of which they suggest might protect against lung and other cancers. They postulate that β-carotene might block UV radiation of the skin by increasing pigmentation or otherwise preventing cutaneous photobiosynthesis of vitamin D_3, a precursor to 1,25-dihydroxyvitamin D, the principal active form of the vitamin. They also observed a weak inverse relationship between total circulating carotenoids and 1,25-dihydroxyvitamin D (*i.e.,* a Pearson correlation coefficient of −0.10) in their own study of 123 participants from the Lipid Research Clinics Coronary Primary Prevention Trial. (4)

To test this hypothesis, we investigated whether chronic supplementation with β-carotene in the ATBC study altered the serum concentrations of either the principal serum circulating form of vitamin D, 25-hydroxyvitamin D, or the principal active metabolite, 1,25-dihydroxyvitamin D.

Materials and Methods

This study was conducted within the ATBC study, which was a joint project of the National Public Health Institute of Finland and the United States National Cancer Institute. The rationale, design, population, and results have been described in detail elsewhere (1, 5). We randomly selected 20 pairs of participants—five from each of four seasons at the time of follow-up blood draw—from those who had a follow-up serum sample available and who were matched (one from the placebo group and one from the group receiving β-carotene alone, that is, not receiving α-tocopherol supplement) on age (in years), month of blood collection at baseline (that is, prerandomization), and duration of time (in months) between baseline and follow-up blood collection (1–5 years after baseline, average 2.4 years). Participants were excluded if they had been diagnosed with cancer or had less than 90% compliance with daily supplementation regimen. Frozen (−70°C) baseline and follow-up serum samples were randomly ordered within the four samples per β-carotene/placebo pair, thawed, and assayed for both 25-hydroxyvitamin D (RIA with I^{125} tracer; Ref. 6) and 1,25-dihydroxyvitamin D (radioreceptor assay; Ref; 7). β-carotene serum concentrations were available for all of the participants at baseline and at follow-up.

A paired *t* test was used to test the hypotheses that the baseline to follow-up changes in 25-hydroxyvitamin D and

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[3] The abbreviation used is: ATBC study, α-Tocopherol, β-Carotene Cancer Prevention Study.

Table 1 Mean and SD serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations before and after β-carotene supplementation

Supplement	*N*	Baseline	Follow-Up	Follow-Up − baseline	β-carotene *vs.* placebo[a] (95% CI)	*P*
25-hydroxyvitamin D (ng/ml)						
β-carotene	20	15.6 (7.0)	19.0 (8.0)	3.5 (9.1)	0.6 (−2.8–4.0)	0.72
Placebo	20	14.9 (5.9)	17.8 (6.3)	2.9 (6.5)		
1,25-dihydroxyvitamin D (pg/ml)						
β-carotene	20	33.1 (9.4)	34.1 (6.6)	1.1 (11.7)	−1.5 (−9.2–6.1)	0.68
Placebo	20	36.6 (9.0)	39.2 (8.1)	2.6 (9.2)		

[a] Difference in vitamin D metabolite concentrations between β-carotene and placebo matched-pair differences (follow-up − baseline); paired *t*-test.

1,25-dihydroxyvitamin D concentrations in the β-carotene supplementation group did not differ from the changes in the placebo group. The Shapiro-Wilk statistic on the normality of the distribution of the difference between the two groups in the metabolite differences over time was 0.75 for 25-hydroxyvitamin D and 0.50 for 1,25-dihydroxyvitamin D. We also measured the Spearman correlation between β-carotene and each vitamin D metabolite at baseline among all of the 40 subjects, as well as the Spearman correlation between β-carotene and each metabolite at follow-up separately for subjects in the β-carotene group and in the placebo group.

Results

In the placebo group, the mean β-carotene level was 167 μg/liter at baseline and 189 μg/liter at follow-up. In contrast, mean serum β-carotene levels in the supplementation group increased from 199 μg/liter at baseline to 3039 μg/liter at follow-up, representing a 15-fold rise.

The mean paired-sample difference between baseline and follow-up 25-hydroxyvitamin D serum levels was 0.6 ng/ml greater in the β-carotene group compared with the placebo group. The difference, however, was not statistically significant (95% confidence interval: -2.8–4.0; $P = 0.72$). For 1,25-dihydroxyvitamin D, the baseline follow-up differences were, on average, 1.5 pg/ml lower in the β-carotene group compared with the placebo group and also did not achieve statistical significance (Table 1). We observed no significant linear correlation between serum vitamin D metabolite and serum β-carotene either at baseline or at follow-up in the placebo or β-carotene groups. At baseline, the Spearman correlation coefficients were 0.29 ($P = 0.07$) for 25-hydroxyvitamin D and −0.02 ($P = 0.90$) for 1,25-dihydroxyvitamin D. At follow-up, the Spearman correlation coefficients in the placebo group were −0.05 ($P = 0.85$) for 25-hydroxyvitamin D and −0.09 ($P = 0.69$) for 1,25-dihydroxyvitamin D; and in the β-carotene group, they were 0.04 ($P = 0.87$) for 25-hydroxyvitamin D and 0.20 ($P = 0.40$) for 1,25-dihydroxyvitamin D.

Discussion

The relative changes in both serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D from baseline to follow-up between the β-carotene supplement and placebo groups were small (approximately +4% and −4% of baseline, respectively) and statistically nonsignificant. Moreover, we observed no significant correlations between serum β-carotene and vitamin D metabolite concentrations among the participants.

Among the bases for the hypothesis that β-carotene may interfere with vitamin D synthesis were cross-sectional data reported by Kritchevsky *et al.* (4) showing a slight negative correlation between circulating total carotenoid levels and 1,25-dihydroxyvitamin D concentrations. By contrast, the present findings derive from a long-term supplementation study in which on-study serum β-carotene levels were substantially elevated (15 times baseline levels). Thus, if β-carotene did interfere with the synthesis of vitamin D metabolites by blocking cutaneous UV radiation absorption or preventing transformation of cutaneous 7-dehydrocholesterol into pre-vitamin D_3, such effects should have been readily observable among the ATBC study participants who received β-carotene supplements and achieved high serum β-carotene concentrations.

Previous studies have found that high-dose β-carotene supplementation does not adversely interact with α tocopherol and several other carotenoids (8, 9). The results of this study provide evidence that β-carotene supplementation also does not interfere with the endogenous production of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D. They further suggest that it is unlikely that an interaction between supplemental β-carotene and vitamin D metabolites contributed to the modest increase in lung cancer incidence observed in the ATBC study.

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